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Original Article

B-Type natriuretic peptide levels predict extent and severity of coronary artery disease in non-ST elevation acute coronary syndrome and normal left ventricular function

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ABSTRACT

Background: B-type natriuretic peptide has been used as a biological marker for prognosis in patients with acute coronary syndrome (ACS). However, a relation between the quantity of BNP levels and the severity of coronary artery disease has not been systematically evaluated.

Methods: 197 patients with ACS without ST elevation with normal LV systolic function were enrolled. BNP was measured in all recruited patients within 12 h of hospitalization. All patients underwent coronary angiography. We correlated BNP levels in patients with unstable angina (USAP) and non ST-elevation myocardial infarction (NSTEMI) with angiographic disease severity including Gensini Score.

Results: BNP levels were significantly higher in the NSTEMI group in comparison to the USAP Group (161 ± 149.3 vs 79.6 ± 94.2 pg/mL; $p < 0.001$). BNP levels rose significantly with increasing number of vessels involved (1-vessel = 51.4 ± 31.6; 2-vessels = 114.0 ± 67.8; 3 vessels = 265.4 ± 188.8 pg/mL, $p < 0.001$). Most importantly, BNP> 80 pg/ml was found to strongly predict the presence of Triple vessel disease (odds ratio 18.87; 95% confidence intervals 5.36–66.36), and Double vessel disease (odds ratio 3.62; 95% confidence intervals 1.75–7.47). In single vessel group, BNP was significantly higher when LAD was involved vessel (64.78 vs 49.76 pg/mL, $p < 0.05$).

Gensini Score showed a strong correlation with BNP levels ($r = 0.675$, $p < 0.01$), and Gensini Score was significantly higher in those with BNP> 80 pg/ml (40.9 ± 29.7 vs 13.4 ± 16.5 $p < 0.001$).

Conclusion: Circulating BNP levels appear elevated in Non ST Elevation ACS, even in the absence of LV systolic dysfunction. High BNP levels are associated with multi-vessel disease and diffuse coronary atherosclerosis.

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1. Introduction

B-type natriuretic peptide (BNP) is a peptide consisting of 32 aminoacids produced by the myocytes as a prohormone. It is released in response to ventricular dilatation and pressure overload, in its active form after peptidase degradation, into the cardiovascular system.[1]

BNP levels are increased after myocardial infarction and high levels are related to an increased risk of adverse events.[2]

Recently it has been demonstrated that BNP and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) also provide predictive information on acute coronary syndromes (ACSs), and they appear related to the severity of CAD in patients affected with ACS.[3,4]

Acute coronary syndromes without ST elevation encompass a wide range of events and have different prognostic values in relation to the type of plaque lesions and the diffusion of coronary atherosclerosis. The risk assessment, based on clinical history and examination, electrocardiographic (ECG) characteristics, and markers of myocardial damage, still remains relatively inaccurate.[5]

The risks of subsequent death and/or recurrent ischemic events also vary widely, depending on the presence of myocardial ischemic areas, irreversible myocyte injury, the hemodynamic consequences of ischemia and the extent of coronary atherosclerosis.

Several studies in ACS patients demonstrated a strong association between increased BNP levels and poor clinical outcome; however, the underlying mechanisms responsible for this association are not well clarified: BNP and pro-BNP could be indicators for multivessel disease, poor TIMI flow, as well as markers of coronary disease extension.[4,6,7]

To support this hypothesis, a few studies has been done but they are limited by their retrospective nature, being a subgroup of a trial, not having information about LV functions or small sample size.[8]

So we planned this study to better assess the role of BNP in assessing severity of CAD in real world practice in a prospective manner with well defined patient inclusion and exclusion criteria among a spectrum of Non ST Elevation ACS Patients.

We compared BNP levels in patients with Unstable angina and Non ST Elevation MI in relation to angiographic lesions, vessel narrowing, and the extension of coronary disease, using Gensini Score.

2. Material and methods

2.1. Study population

The study was performed on the 197 consecutive subjects (males-154, females-43) who presented to our department with ACS with no ST elevation, and underwent coronary artery angiography in our Department from May 2012 to Feb 2013.

UA was defined by ECG ST segment depression or prominent T-wave inversion with negative Troponins with any of the following:

- Rest angina – lasting for 20 min or more
- New onset angina – of at least CCS class 3 severity started in preceding one month
- Increasing Angina – previously diagnosed angina that has become distinctly more frequent, longer in duration or lower in threshold (i.e. increased by 1 or more CCS class to at least class 3 severity).[9]

NSTEMI was diagnosed when an elevation of troponin-I levels (more than 1.0 ng/ml in any sample during the first 12 h post-admission) occurred, with or without ST/T changes in the ECG, in the presence of features of UA.[9]

Patients were evaluated prior to blood sampling to determine their heart failure status according to the New York Heart Association. All recruited patients underwent echocardiographic examination (Philips IE33) to evaluate wall motion abnormality, left ventricular morphology and systolic functions.[10] Blood samples for BNP were performed within 12 h of hospital admission and written informed consent was obtained from all patients. coronary angiography was performed within first 3 days of hospital admission. Study was approved by local research ethical committee.

2.1.1. Exclusion criteria

Patients with a history of myocardial infarction, ST elevation on admission ECG, Evolution of ECG showing New LBBB or New Q waves, valvular disease, acute or chronic heart failure, cardiomyopathy, systolic dysfunction with ejection fraction <50%, renal, liver, neoplastic, inflammatory and infectious diseases were excluded.

2.2. Treatment protocol

All patients underwent standard therapy as per discretion of treating cardiologist.

2.3. Laboratory assays

Plasma BNP and Troponin-I were immediately analyzed on the same EDTA-anti-coagulated blood sample collected on admission using the quantitative immunofluorescence assay manufactured by Biosite (San Diego, CA, USA). The analytic sensitivity of the BNP assay is <5 pg/Ml and for Troponin-I is <0.1 ng/ml.

2.4. Angiographic analysis

All coronary angiograms were evaluated at the angiographic core laboratory by physicians who were blinded to the patient's clinical or BNP status.

Coronary stenosis was quantified using validated quantitative coronary angiography by the consensus opinion of two experienced interventional cardiologists with >50% diameter stenosis considered as significant. Assessment of epicardial coronary flow was done using the TIMI flow grade according to established methods.[11] The Gensini Score (GS) was used to assess the burden of coronary arteriosclerosis.[12] The GS system yields a qualitative and quantitative evaluation of the coronary angiogram; it grades the narrowing of the lumen of the coronary artery as 1 for ≤25% narrowing, 2 for 26–50%

narrowing, 4 for 51–75% narrowing, 8 for 76–90% narrowing, 16 for 91–99% narrowing, and 32 for total occlusion. This primary score is multiplied by a factor that takes into account the importance of the position of the lesion in the coronary arterial tree (5 for the left main coronary artery, 2.5 for the proximal left anterior descending artery or proximal left circumflex artery and 1.5 for the mid-region, 1 for the distal left anterior descending artery, and 1 for the mid-distal region of the left circumflex artery or right coronary artery). In our study, the GS was expressed as the sum of the scores for all three coronary arteries in order to evaluate the entire extent of CAD.

2.5. *Statistical analysis*

The statistical analysis was performed using the SPSS software for Windows, version 13.0 (SPSS, Inc., Chicago). Summary statistics for continuous variables were recorded as the mean ± SD and the categorical data was summarized as frequencies and percentages. Correlations between continuous variables were calculated according to Spearman-Rho. logistic regression analysis was performed with the extent of CAD, smoking, diabetes, hypertension and dyslipidemia as the dependent variable and BNP level as independent variable. odds ratio (OR) is presented with 95% confidence intervals. All numeric data are presented as the mean ± SD, and a p value of less than 0.05 was considered statistically significant.

3. Results

3.1. *BNP and clinical presentation*

Clinical characteristics and associated risk factor are reported in (Table 1). BNP levels were significantly higher in the NSTEMI Group in comparison to the USAP Group and (161 ± 149.3 vs 79.6 ± 94.2 pg/mL; $p < 0.001$).

BNP >80 pg/mL was recruited in 39 of 58 (68%) patients of NSTEMI while 54 of 139 (39%) of USAP patients were recruited. Triple vessel disease was revealed more frequently in patients with BNP >80 pg/mL – 32 out of 35 (91%) patients of Triple vessel disease had BNP >80 pg/ml. Except for hypertension which was more common in patients with BNP >80 pg/ml, other risk factors were equal in both groups (Table 2).

3.1.1. *BNP and coronary vessel involvement*

BNP was strictly related to the extent of coronary disease: significant progressive differences were assessed between the 1-vessel group, the 2-vessel and 3-vessel group (1-vessel 51.4 ± 31.6; 2-vessel 114.0 ± 67.8; 3 vessel 265.4 ± 188.8 pg/mL, $p < 0.001$). A similar significant trend was found between the 1-vessel group and the 2-vessel. group ($p < 0.01$), 2-vessel group and 3-vessel group ($p < 0.01$). When the measurement was limited to the 1-vessel group ($n = 117$), we observed a significantly higher BNP in patients with left anterior descending artery (LAD) involvement than in patients with other coronary artery involvement (64.78 vs 49.76 pg/mL, $p < 0.05$) (Table 3).

The analysis of the Gensini Score (GS) demonstrated a strong correlation between coronary artery disease extension and BNP levels ($r = 0.675$, $p < 0.01$) (Fig. 1). Gensini Score was significantly higher in those with BNP> 80 vs < 80 pg/ml (40.9 ± 29.7 vs 13.4 ± 16.5 $p < 0.001$).

BNP> 80 pg/ml was found to strongly predict the presence of TVD (odds ratio 18.87; 95% confidence intervals 5.36–66.36), and DVD (odds ratio 3.62; 95% confidence interval 1.75–7.47) but also associated with hypertension (odds ratio 2.67; 95% confidence intervals 1.28–5.59) (Table 4).

Table 1 – Clinical characteristics and risk factors.

	USAP ($n = 139$)	NSTEMI ($n = 58$)	p value
NO.	139	58	–
Male	106 (76.3)	48 (82.8)	0.314
Diabetes (n)	15 (10.8)	10 (17.2)	0.215
Hypertension (n)	47 (33.8)	29 (50.0)	0.033
Smoking (n)	85 (61.2)	40 (69.0)	0.299
Dyslipidemia (n)	70 (50.4)	21 (36.2)	0.069
BNP (pg/ml) mean ± SD	79.7 ± 94.2	161.4 ± 149.3	<0.001

Table 2 – Clinical characteristics and associated risk factors in patients with BNP < 80 and > 80 pg/ml.

	BNP <80 ($N = 104$)	BNP >80 ($N = 93$)	P value
Age (mean ± SD)	52.7 ± 10.4	54.3 ± 11.5	0.332
Diabetes (%)	11 (10.6)	14 (15.1)	0.345
Hypertension (%)	31 (29.8)	45 (48.4)	0.008
Smoking (%)	63 (60.6)	62 (66.7)	0.375
Dyslipidemia (%)	41 (44.1)	44.09	0.575
USAP (%)	85 (81.7)	54 (58.1)	0.012
NSTEMI (%)	19 (18.3)	39 (41.9)	0.0003
Triple vessel disease (no.)	03	32	<0.001
Gensini Score (mean ± SD)	13.4 ± 16.5	40.9 ± 29.7	<0.001

4. Discussion

Many studies have shown that the elevation of BNP levels, as well as NT-proBNP levels, obtained after the acute phase in patients with a broad range of ACS independently predicts mortality. However, in most of the reports, authors did not distinguish between subjects with low ejection fraction and LV enlargement.[3,4,13] Because of its release in response to increased ventricular chamber pressure or wall tension, in ACS patients with decreased LV ejection fraction, elevated BNP levels reflect a high degree of myocardial dysfunction, with a higher risk of death and congestive heart failure.

The main finding of our study is that BNP levels are related also to the severity of coronary atherosclerosis: patients with multi-vessel disease showed higher BNP levels than subjects with only one or two vessel involvement. This trend was

Table 3 – BNP and extent of CAD.

	SVD	DVD	TVD	p value
No	117	45	35	
BNP (pg/ml)	51.9 ± 31.9	114.0 ± 67.8	265.4 ± 188.8	<0.001
Gensini Score	13.4 ± 9.9	35.6 ± 26.3	58.80 ± 35.5	0.007

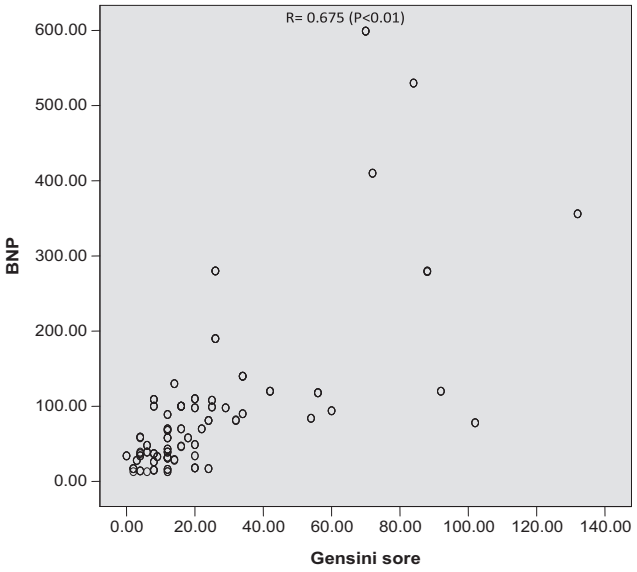

Fig. 1 – Correlation of BNP and Gensini Score.

confirmed independently of the diagnosis of USAP or NSTEMI. Elevation of BNP levels appears strictly related to coronary artery disease.

Our results are in accordance with those of Sadanandan et al showing a correlation between TIMI flow, tightness of culprit stenosis and BNP levels.[8] However, with respect to the cited study, our sample was characterized by the absence of left ventricular dysfunction and enlargement, which are the main factors responsible for BNP increase.[14,15] Again, we demonstrated that BNP threshold of 80 pg/ml appears able to predict the extension of coronary disease independently from LV systolic dysfunction and enlargement. The same value has been previously recognized as cutoff for mortality and risk for adverse events in patients with ACS.[3,4,8] Our results are also in accordance with study by Alberto Palazzuoli et al[16] but the cited study was retrospective in nature.

Most importantly our study strongly showed that high BNP (>80 pg/ml) is a strong predictor of Triple vessel disease irrespective of diagnosis of USAP or NSTEMI. The exact mechanisms of natriuretic peptides rise in coronary disease are not completely understood. Ischemia may constitute an independent stimulus for BNP release towards a transient decrease of systolic function and compliance, reflecting not only the impairment in left ventricular function, but also the severity of the ischemic insult.[17] Alternatively, BNP secretion may be due to the augmented regional wall stretch which occurs during ischemic attacks even in the absence of pump dysfunction inducing the neurohormonal activation.[18] The detection of BNP gene expression in ischemic and infracted regions together with BNP receptor recruitment in coronary plaques could explain a novel mechanism of BNP induction.[19,20]

The strong correlation between the Gensini Score and BNP levels extend previous findings demonstrating that a further stimulus for BNP increase could be the severity and diffusion of coronary plaques that, consistent with this observation, lead to a worsening of the ischemic myocardial area.[18,21]

All together these data could explain the mechanisms linking BNP to an adverse outcome in CAD, it represents a marker of coronary disease severity and is related to the presence of plaques diffusion and narrowing. For the above mentioned reasons BNP should be considered as an indicator of regional ischemia and as a predictor for adverse events in patients with chest pain.[22,23]

Table 4 – Age and sex adjusted prevalence of traditional risk factors & CAD magnitude (odd ratio, 95% confidential intervals, logistic regression) in high BNP patients (>80) compare to low BNP level (BNP ≤80).

Variables	BNP>80 ($n = 93$)	BNP ≤80 ($n = 104$)	p value
Diabetes	1.65 (0.69–3.94)	1	0.257
Hypertension	2.67 (1.28–5.59)	1	0.009
Smoking	1.25 (0.64–2.46)	1	0.509
Dyslipidemia	0.86 (0.49–1.52)	1	0.616
SVD	0.95 (0.05–0.19)	1	<0.001
DVD	3.62 (1.75–7.47)	1	<0.001
TVD	18.87 (5.36–66.36)	1	<0.001

5. Study limitations

The present study suffers from few limitations, the major one is the small sample size. However our sample was carefully defined and selected on the basis of echocardiographic and clinical criteria. Age and sex could have influenced the findings even if the population studied had almost similar demographic characteristics in all groups. We did not compare BNP levels to other biomarkers of myocardial injury such as Troponin, high sensitive CRP or cytokine levels.

6. Conclusions

BNP represents a biomarker for left ventricular dysfunction and enlargement as well as for myocardial ischemia. It appears it is able to give additional prognostic information to existing traditional biomarkers (i.e. troponin and C-reactive protein). BNP is a candidate for entry into the setting of principal risk scores. Our findings indicate that the level of BNP may reflect the extent or severity of ischemic insult even when irreversible injury and systolic dysfunction have not occurred and strongly predict the presence of Triple vessel disease.

Conflicts of interest

All authors have none to declare.

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